Theoretical Study of a Vanadate Peptide Complex

MICHAEL BÜHL
Organisch-Chemisches Institut, Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Received 15 September 1998; accepted 20 January 1999

ABSTRACT: Optimized geometries (BP86/I) and ^{51}V-NMR chemical shifts (GIAO-B3LYP/I) are reported for selected [VO(OH)(OH_2)(glygly′)] isomers, deprotonated forms thereof, and [VO(OH)(glygly′)] (glygly′ = $H_2N—CH_2—CO—N—CH_2—COO$). The $\delta(^{51}V)$ values are quite sensitive to structural details in the first and second coordination spheres of the vanadium center. In the deprotonated forms, the water molecule is not bound to vanadium, suggesting that the coordination geometry about vanadium can be sensitive to the pH value. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 1254–1261, 1999

Keywords: density functional theory; ^{51}V; chemical shift calculations; peptide complex

Introduction

Even though vanadium plays an important role in the biosphere,[1–3] detailed knowledge of key structures or mechanisms involved remains fragmentary. For instance, the action of vanadium-containing haloperoxidase[4] or nitrogenase[5] enzymes, the binding of vanadium to transferrins,[6] or the way vanadate acts as an insulin mimetic[7] are far from being fully understood. For a deeper insight into possible elementary processes, much research effort is being devoted to the study of simpler model compounds containing small peptides in the coordination sphere of vanadium. Despite a decade of extensive investigations of vanadate peptide complexes,[8–11] only a handful of such compounds are structurally characterized.[9c–11] Direct structural evidence is still lacking for the simplest complexes produced in the reaction of vanadate(V) with dipeptides.[8, 9a]

For these complexes, as for vanadium(V) species in general, ^{51}V-NMR spectroscopy[12] has proven to be an invaluable analytical tool.[13] With the breakthrough in chemical-shift computations based on density functional theory (DFT),[14, 15] this property can now be calculated fairly accurately for transition-metal compounds, hitherto a challenging class for conventional *ab initio* theory. For a number of organic and inorganic vanadium compounds, ex-

Correspondence to: M. Bühl; e-mail: buehl@oci.unizh.ch.

CCC 0192-8651 / 99 / 121254-08

perimental $\delta(^{51}V)$ data have recently been well reproduced at DFT levels.[14,16] When NMR spectra are known but not the nature of the species producing them, theoretical computations of the NMR parameters (in particular, the chemical shifts) can constitute an additional independent source of structural information.[17] For instance, DFT-based calculations of ^{57}Fe chemical shifts for heme model compounds have recently been used to refine structural parameters of the corresponding subunits in larger proteins.[18] In the present study, vanadate complexes with the smallest dipeptide, glycylglycine, are investigated as a first step toward the modeling of the bonding modes of peptides in such complexes and the consequences for the chemical shifts.

The objective of this study is thus twofold: first, the structural proposals forwarded earlier for vanadate-peptide complexes[8b,9a] is validated by geometry optimizations and chemical-shift calculations involving the simplest dipeptide, glycylglycine. Second, it is probed to what extent the computed ^{51}V chemical shifts depend on changes in the first and second coordination sphere of the vanadium center. Special attention is paid to the effect of proton loss, which may occur under physiological conditions.

Computational Details

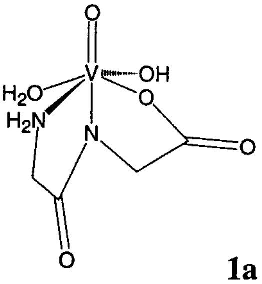
Geometries were fully optimized without symmetry constraints (except where otherwise noted) employing the gradient-corrected exchange-correlation functionals of Becke[19] and Perdew,[20] together with a fine integration grid (75 radial shells with 302 angular points per shell) and basis I (i.e., Wachters' (14s11p6d)/[8s7p4d] all-electron basis augmented with one additional diffuse d and two 4p functions for V,[21] and standard 6-31G* basis set[22] for all other elements (denoted BP86/I). Geometries optimized at this or at comparable levels are usually in good accord with experiment.[16,23] Magnetic shieldings were computed with the gauge-including atomic orbitals (GIAO)-DFT method as implemented[24] in the Gaussian 94 program,[25] employing basis I and the B3LYP combination of functionals, i.e. Becke's three-parameter exchange DFT/Hartree–Fock hybrid functional[26] together with the correlation functional of Lee, Yang, and Parr.[27] This method has proven to be particularly well suited for chemical shifts of several transition-metal nuclei.[16,28] Chemical shifts are reported relative to $[VOCl_3]$, the experimental standard, with a computed absolute shielding of −2317 ppm at the same level.[16] All computations were performed with the Gaussian 94 package.[25] In addition, for selected molecules topological analyses[29] of the total electron density (BP86/I density) were performed using the MORPHY program[30] in order to identify chemical bonds by locating bond paths and bond critical points (bcps).

For anionic complexes, the chemical-shift calculations employed basis I augmented by a set of diffuse s and p functions on the ligand atoms,[31] denoted basis I+. Test calculations indicated a small effect of these diffuse functions for neutral species (cf. the B3LYP/I+ absolute shielding for $[VOCl_3]$, −2319 ppm), but a larger one for anions such as $H_2VO_4^-$ (cf. $\delta_{calc} = -641$ and -629 with basis I and I+, respectively).

Results and Discussion

NEUTRAL SPECIES

From detailed studies of the reaction of vanadate(V) with dipeptides the following requirements for complex formation (in the absence of functionalized side chains) were inferred[8a,9a]: the peptide must contain a terminal primary or secondary amine, an unsubstituted nitrogen in the peptide bond, and a carboxylate group. As a structural model for the resulting complexes, an octahedral arrangement about vanadium was assumed involving four oxygen donor atoms (comprising one from the peptide carboxylate, one water molecule, one oxo group, and one hydroxyl group) and the two nitrogen donor atoms from the peptide.[9a] From the second requirement it is likely that the amide hydrogen of the peptide is lost upon complex formation; thus, $[VO(OH)(OH_2)(glygly')]$ (**1**, glygly' = $H_2N—CH_2—CO—N—CH_2—COO$) appeared to be a plausible target molecule for a theoretical study.[8b]

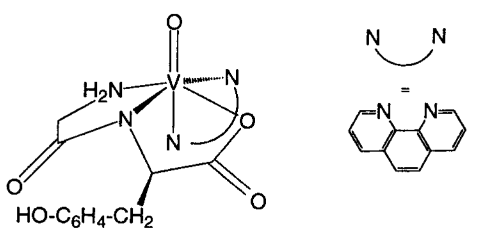


1a

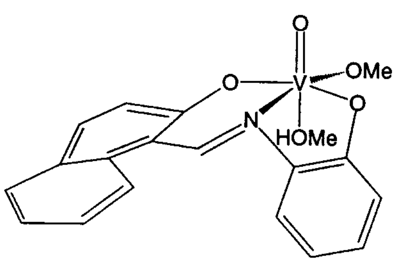
Several arrangements of the ligands can be envisaged; the first geometry optimization started from an initial placement depicted in **1a** (i.e., with a *fac* configuration of the tridentate glygly′ ligand, as implicitly assumed earlier).[9a] In the final, optimized geometry, however, three of the donor atoms (the two nitrogen atoms and the water molecule) exchanged places, apparently without any energy barrier, affording a *mer* configuration of the peptide (**1b**, Fig. 1).

The same *mer* configuration was recently identified in the vanadate(IV) dipeptide complex [VO(glytyr)(phen)] (**2**) and in a related vanadate(V) Schiff-base complex **3**.[32] The latter also includes a labile methanole ligand in the same position as the water molecule in **1b** (i.e., trans to the oxo substituent).

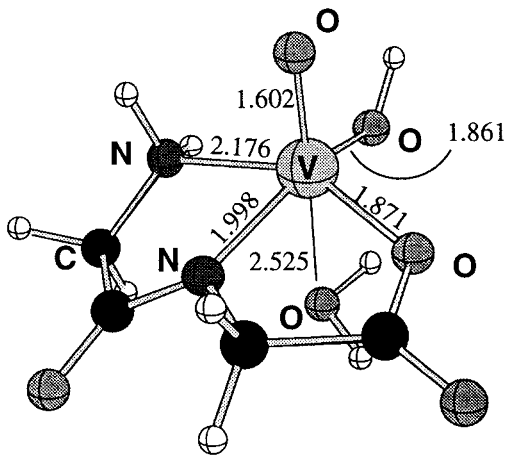
In view of these experimental findings, there remains little doubt that **1b** is a plausible description of the vanadate + glycylglycine reaction product. This notion is corroborated by the excellent accord between the ^{51}V chemical shift computed for **1b**, $\delta = -502$ (Table I), and the experimental value, $\delta = -505$.[9a] This degree of agreement may to some extent be fortuitous (deviations on the order of 100 ppm are possible with the present approach, precluding an unequivocal assignment), but it certainly does not argue against the formulation as **1b** (see, however, the section on anionic species section).



2



3



1b

FIGURE 1. BP86 / I optimized geometry of **1b**.

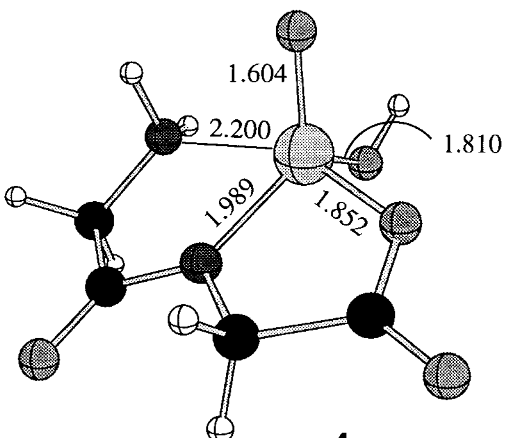
The very long V–OH_2 distance of 2.52 Å in **1b** (Fig. 1) would suggest that the water molecule is quite loosely bound. In the Schiff-base complex **3**, the coordinated methanol molecule is much closer to the vanadium center at 2.131(2) Å.[32,33] However, removal of the water molecule from **1b** costs more than 46 $kJ \cdot mol^{-1}$ at the BP86/I level. In the resulting pentacoordinate species [VO(OH)(glygly′, **4**, Fig. 2)], considerable relaxation of the bonds to vanadium has taken place (e.g., the vanadium-hydroxyl distance decreases by 5 pm in going from **1b** to **4**). In the same sequence, the ^{51}V resonance is predicted to be noticeably shielded to $\delta = -531$ (Table I, δ_{iso} value). That the water molecule is directly bonded to the vanadium atom (and not just to the hydroxyl and carboxyl groups via hydrogen bonds) is evident from the occurrence of a bcp and a bond path between vanadium and the corresponding oxygen atom. The bonding is weak, though, as evidenced by the finding that the values of both ρ and $-\nabla^2\rho$ at this bcp are quite small (0.027 and 0.101 au, respectively), for instance, smaller by one order of magnitude than the corresponding values at the bcp between vanadium and the oxo substituent (0.265 and 0.973 au, respectively).

In **1b** the amide nitrogen atom is coordinated to the vanadium center via the sp^2 lone pair. Can a "normal" amide nitrogen atom (i.e., one still bearing the hydrogen atom) coordinate at all to the vanadium center? To address this question, a proton was removed from the water molecule in **1b** and placed on the amide nitrogen atom. In the

TABLE I.
Computed (GIAO-B3LYP)[a] Isotropic ^{51}V Chemical Shifts δ_{iso} and Principal Tensor Components δ_{ii}^{b} of Vanadate Glycylglycine Complexes.

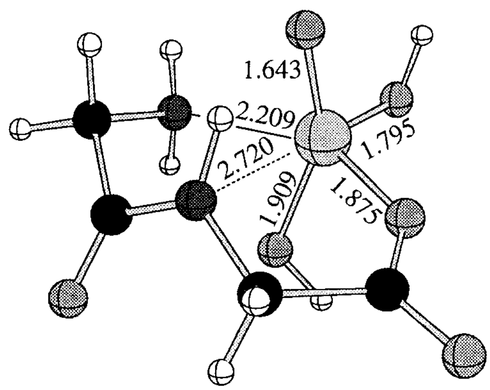
Species[c]	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	α[d]	β[d]	γ[d]
Vanadate + glycylglycine expt	−505[e]						
1b [VO(OH)(OH$_2$)(glygly′)]	−502	−268	−339	−925	11.0	100.1	90.1
4 [VO(OH)(glygly′)]	−531	−184	−392	−1019	2.1	87.4	99.5
1c [VO(OH)$_2$(glygly)]	−459	−76	−458	−845	10.7	85.4	113.1
7a [V(O)$_2$(glygly′)]$^-$ · H$_2$O	−602	−259	−331	−1215	1.5[f]	104.5	64.6
7b [VO(OH)$_2$(glygly′)]$^-$	−485	+83	−303	−1236	21.4	91.0	83.1
7c [VO(OH)(glygly″)]$^-$ · H$_2$O	−316	−77	−196	−674	26.2	100.4	124.1

[a] Basis I for neutral species **1** and **4**; basis I+ for anions **7**.
[b] In parts per million relative to [VOCl$_3$].
[c] glygly = H$_2$NCH$_2$—CO—NH—CH$_2$COO, glygly′ = H$_2$NCH$_2$—CO—N—CH$_2$COO, glygly″ = HNCH$_2$—CO—N—CH$_2$COO.
[d] Orientation of the principal axes: α is the angle in degrees between the vector along δ_{11} and the bond between V and the terminal amine N atom, β is the angle between the vector along δ_{11} and V=O bond, and γ is the angle between the vector along δ_{22} and the bond between V and the coordinated carboxylate O atom.
[e] From ref. 9(a).
[f] Angle between the vector along δ_{11} and the bond between V and the coordinated carboxylate O atom.



4

FIGURE 2. BP86 / I optimized geometry of **4**.



1c

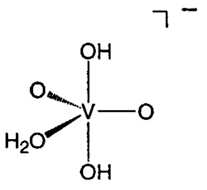
FIGURE 3. BP86 / I optimized geometry of **1c**.

resulting optimized structure (**1c**, Fig. 3) the amide moiety has apparently dissociated from the metal with a V ··· N separation larger than 2.7 Å. Topological analysis of the electron density, however, still indicates the presence of a bcp and a bond path and thus a bonding interaction between these two atoms. The change in the first coordination sphere about vanadium in going from **1b** to **1c** is also reflected in a noticeable deshielding to $\delta(^{51}V) = -459$ (Table I).

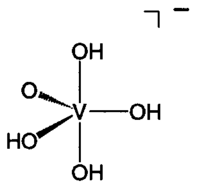
At the BP86/I level, **1c** is higher in energy than **1b** by 50.6 kJ · mol^{-1} (56.5 kJ · mol^{-1} at B3LYP/I). Species **1c** may thus represent a viable intermediate in the reaction between vanadate and glycylglycine, arising formally from a condensation of hypothetical H_3VO_4 and the dipeptide. The subsequent reaction to **1b** could then proceed with a considerable driving force via a single (and presumably fast) proton transfer.

ANIONIC SPECIES

Aqueous vanadates are very complex systems consisting of monomeric and oligomeric species in variable amounts, depending on pH and concentration.[34] Under physiological conditions (i.e., pH 7 and very low concentration) vanadium in the oxidation state V is predominantly present as dihydrogenvanadate, $H_2VO_4^-$ (**5**). A four-coordinate tetrahedral arrangement as in the parent deprotonated VO_4^{3-} is usually presumed,[35] but evidence



6a



6b

from UV-VIS and MCS spectra was also interpreted in terms of a pentacoordinate hydrate (**6a**) with one additional water molecule in the coordination sphere.[36] More recent thermodynamic data, on the other hand, argue against such an increase in coordination number at this stage.[37]

All attempts to optimize a structure resembling **6a** resulted in expulsion of the water from the coordination sphere,[38–40] affording a tetrahedral ligand arrangement and an externally hydrogen-bonded water molecule. Likewise, no minimum corresponding to a $[V(O)_2(OH)_2(OH_2)_2]^-$ species (i.e., containing two additional water molecules) could be located. The resulting minima of lowest energy can be described as $\mathbf{5} \cdot H_2O$ and $\mathbf{5} \cdot 2H_2O$ and are depicted in Figure 4. Pentacoordinate **6b**, an isomer of **6a**, was previously considered as a transition-state analogue for a phosphorane.[41] At the BP86/I level, however, this isomer is 83.3 $kJ \cdot mol^{-1}$ higher in energy than $\mathbf{5} \cdot H_2O$.

The experimental ^{51}V chemical shift of **5** is $\delta = -560$.[9a] For isolated **5** (C_2 symmetry) $\delta(^{51}V) = -629$ is computed, apparently not in very good accord with the experiment. However, adding water molecules has a notable effect, because $\delta = -591$ and -565 are obtained for $\mathbf{5} \cdot H_2O$ and $\mathbf{5} \cdot 2H_2O$, respectively. The latter value is in fact very close to the experiment, but this may again be partly fortuitous. More water molecules should be added until the result is converged.[42] Nevertheless, these results indicate that solvent effects on $\delta(^{51}V)$ can be substantial, at least for anionic species.

Turning now to the peptide complex, one may ask if **1b**, analogous to vanadate itself, would rather exist as its conjugate base at pH 7 (i.e., in the deprotonated, anionic form) as was suggested previously.[8b,c] The most acidic proton in **1b** is certainly that of the hydroxyl group at vanadium. When this proton is removed and the structure relaxed, the loosely bonded water molecule leaves the vanadium center altogether and remains attached via only a hydrogen bond (**7a**, Fig. 5). The coordination geometry about vanadium in **7a** can be viewed as that of a distorted trigonal bipyramid with the amide nitrogen and the two oxo atoms in the equatorial positions. This arrangement is quite similar to that found in the active site of a vanadium-containing haloperoxidase containing three equatorial oxo substituents.[4b]

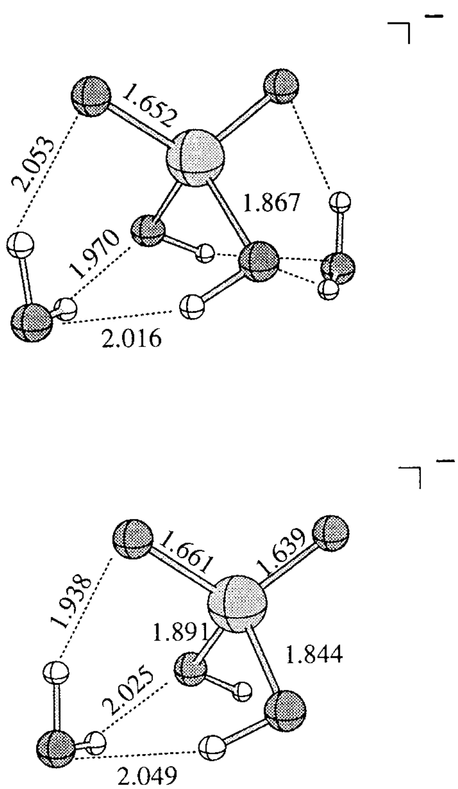


FIGURE 4. BP86/I optimized geometries of $\mathbf{5} \cdot H_2O$ (bottom) and $\mathbf{5} \cdot 2H_2O$ (C_2 symmetry, top).

At the BP86/I level, the proton affinity (PA) of **7a** is lower than that of **5** by 83.3 $kJ \cdot mol^{-1}$. Thus, isolated **1b** would be a stronger acid than hypothetical H_3VO_4 and it could be expected that the vanadate-glycylglycine complex should be formulated as **7a** rather than as **1b** at pH 7. Solvation is likely to attenuate the PAs of **7a** and **5a**, however (the negative charge in **7a** is to some extent already stabilized by "internal solvation" due to the polarizable peptide moiety), so that the energies for isolated species are probably not conclusive. The same holds true for the computed $\delta(^{51}V)$ values, given the solvation effect noted above for **5**. The ^{51}V chemical shift computed for **7a**, $\delta = -602$, compares less favorably to the experiment ($\delta = -505$) than that for **1b** (Table I). If further solvation would result in deshielding of the ^{51}V

nucleus in anionic **7a** (as for **5**), agreement with the experiment would improve.[43]

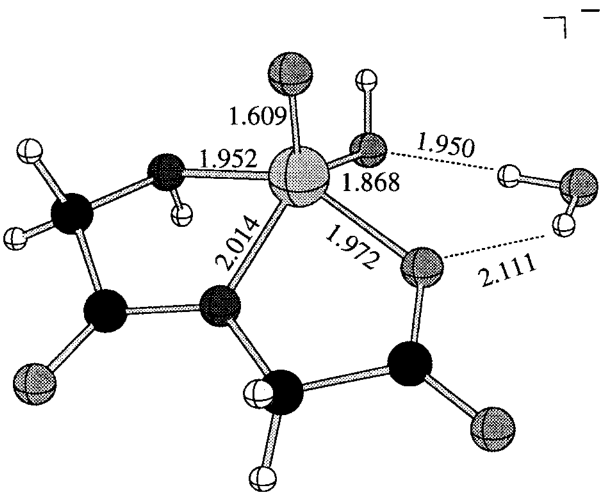
As noted above, a definite assignment of the experimental resonance to a particular structure based on the NMR calculations appears to be difficult at this point. In any event, the present calculations suggest that the coordination geometry about vanadium can be quite sensitive to the pH value (at least when this involves protonation and deprotonation at an atom directly bonded to vanadium), which is certainly an intriguing possibility.

Two other sites of deprotonation were investigated, namely, the coordinated water molecule and the amine moiety. Proton abstraction from the former affords **7b** (Fig. 5), which is 52.3 $kJ \cdot mol^{-1}$ higher in energy than **7a** (BP86/I level). In **7b** the sixfold coordination about vanadium is retained, but the orientation of the ligands is reminiscent of a pentagonal pyramid rather than an octahedron. A similar coordination sphere is realized in $[VO(O_2)(glygly')]^-$.[9c] Deprotonation of the amino group is slightly less favorable energetically (10.9 $kJ \cdot mol^{-1}$ compared to **7b**); in the resulting **7c** (Fig. 5), as with **7a**, the water molecule is expelled from the vanadium center.

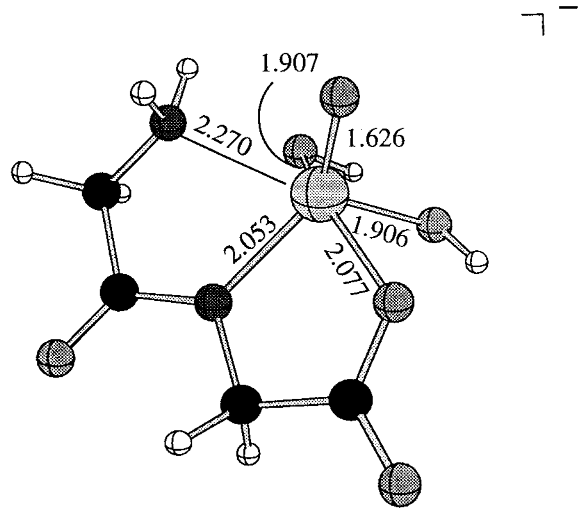
Deprotonation of ligands at vanadium apparently makes them better donors; as a result, the weakly coordinated water molecule cannot compete any more for the vacant d orbitals at the metal and remains only hydrogen-bonded.

Compared to **7a**, the ^{51}V nucleus in both **7b** and **7c** is considerably deshielded (Table I). The chemical shift predicted for **7c**, $\delta(^{51}V) = -316$, is particularly noteworthy, because the first coordination sphere is quite similar to that in **4** and **7a** for which clearly different shifts are obtained ($\delta_{iso} = -531$ and -602, respectively, see Table I). Isomer **7c** can thus be excluded on the grounds of both relative energies and chemical shifts.

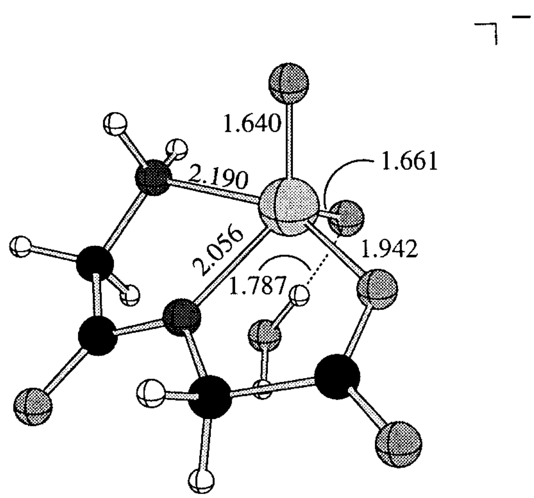
In addition to the isotropic $\delta(^{51}V)$ data, the principal tensor components δ_{ii} are included in Table I. In general the calculated orientation of the shift tensor is such that the most deshielded components, δ_{11} and δ_{22}, are approximately perpendicular to the terminal V = O bond with δ_{11} pointing roughly toward the terminal amine N atom. A number of ^{51}V chemical-shift tensor data are available experimentally, mostly for vanadium oxide phases but also for oxovanadium(V) species.[44,45] For the latter (with other oxygen donors at vanadium) the δ_{ii} values span the range between circa $\delta = -50$ and -1150 (i.e., similar to those computed for neutral and anionic species **1**, **4**, and **7** in Table I). A detailed analysis of these



7c



7b



7a

FIGURE 5. BP86 / I optimized geometries of (from bottom to top) **7a**–**7c**.

numbers is difficult, however, because all principal values (and sometimes also the orientation) change unsystematically in going from one species to another.

Conclusions

Based on previous structural proposals for the products of the reaction of vanadate with dipeptides, plausible candidates were identified for the glycylglycine derivative by DFT-based geometry, energy, and ^{51}V chemical-shift calculations. Experimental $\delta(^{51}V)$ data can be reconciled with neutral, hexacoordinate $[VO(OH)(OH_2)(glygly')]$ or with its anionic conjugate base, pentacoordinate $[V(O)_2(glygly')]^- \cdot H_2O$. In the latter, the water molecule is not coordinated to vanadium, pointing to the interesting possibility that the coordination geometry about the metal could be sensitive to and possibly even tunable by the pH value.

Changes in the first or second coordination sphere of vanadium (by removal of the water ligand or by proton loss or transfer) produced notable changes in the computed ^{51}V chemical shifts, which span the range from $\delta \approx -300$ to -600. Large variations (up to $\Delta\delta \approx 70$) were also found for the $\delta(^{51}V)$ values of the reactant vanadate, $H_2VO_4^-$, upon microsolvation by one or two water molecules. Thus, solvation may be an important factor governing the chemical shifts and further theoretical studies should be extended to larger, hydrated clusters of vanadate and its peptide complexes.

Acknowledgments

The author wishes to thank W. Thiel for his continuous support and D. C. Crans, H. D. Rehder, and A. S. Tracey for their interest in this work and for helpful comments and suggestions. Calculations were carried out on a Silicon Graphics PowerChallenge (Organisch-Chemisches Institut, Universität Zürich) and IBM RS6000 workstations (C4 cluster, ETH Zürich), as well as on a NEC-SX4 (CSCS, Manno, Switzerland).

References

1. Sigel, H.; Sigel, A., Eds.; Metal Ions in Biological Systems; Marcel Dekker: New York, 1995; Vol. 31.
2. (a) Chasteen, N. D., Ed.; Vanadium in Biological Systems; Kluwer Academic Publishers: Amsterdam, 1990. (b) Tracey, A. S.; D. C. Crans, Eds.; Vanadium Compounds—Chemistry, Biochemistry, and Therapeutic Applications, ACS Symposium Series, Vol. 711, Washington DC, 1998.
3. Rehder, D. Angew Chem Int Ed Engl 1991, 30, 148.
4. (a) Vilter, H. In Metal Ions in Biological Systems; Sigel, H.; Sigel, A., Eds.; Marcel Dekker: New York, 1995; Vol. 31, p 325; X-ray structure: (b) Messerschmidt, A.; Wever, R. Proc Natl Acad Sci USA 1996, 93, 392.
5. (a) Eady, R. R. In Metal Ions in Biological Systems; Sigel, H.; Sigel, A., Eds.; Marcel Dekker: New York, 1995; Vol. 31, p 363; (b) Eady, R. R. Polyhedron 1989, 8, 1695.
6. Butler, A.; Carrano, C. J. Coord Chem Rev 1991, 109, 61.
7. (a) Orvig, C.; Thompson, K. H.; Battell, M.; McNeill, J. H. In Metal Ions in Biological Systems; Sigel, H.; Sigel, A., Eds.; Marcel Dekker: New York, 1995; Vol. 31, p 575; (b) Srivastava, A. K.; Chiasson, J.-L., Eds. Molecular and Cellular Biochemistry; Kluwer Academic Publishers: Boston, 1995; Vol. 153.
8. (a) Rehder, D. Inorg Chem 1988, 27, 4312; (b) Crans, D. C.; Holst, H.; Keramidas, A. D.; Rehder, D. Inorg Chem 1995, 34, 2524; (c) Fritzsche, M.; Elvingston, K.; Rehder, D.; Pettersson, L. Acta Chem Scand 1997, 51, 483.
9. (a) Jaswal, J. S.; Tracey, A. S. Can J Chem 1991, 69, 1600; (b) Jaswal, J. S.; Tracey, A. S. J Am Chem Soc 1993, 115, 5600; (c) Einstein, F. W. B.; Batchelor, R. J.; Angus−Dunne, S. J.; Tracey, A. S. Inorg Chem 1996, 35, 1680.
10. Keramidas, A. D.; Miller, S. M.; Anderson, O. P.; Crans, D. C. J Am Chem Soc 1997, 119, 8915.
11. Tasiopoulos, A. J.; Deligiannakis, Y. G.; Woollins, J. D.; Slawin, A. M.; Kabanos, T. A. J Chem Soc Chem Commun 1998, 569.
12. (a) Horwath, O. W. Prog NMR Spectrosc 1990, 22, 453; (b) Rehder, D. In Transition Metal Nuclear Magnetic Resonance; Pregosin, P. S., Ed.; Elsevier: Amsterdam, 1991; p 1.
13. Even the binding to large proteins such as the transferrins can be studied with ^{51}V NMR: Saponja, J. A.; Vogel, H. J. J Inorg Biochem 1996, 62, 253.
14. Malkin, V. G.; Malkina, O. M.; Casida, M. E.; Salahub, D. R. J Am Chem Soc 1994, 116, 5898.
15. (a) Schreckenbach, G.; Ziegler, T. Theor Chem Acc 1998, 2, 71; (b) Bühl, M.; Kaupp, M.; Malkin, V. G.; Malkina, O. L. J Comput Chem, 1999, 20, 91.
16. Bühl, M.; Hamprecht, F. A. J Comput Chem 1998, 19, 113.
17. (a) Cremer, D.; Olsson, L.; Reichel, F.; Kraka, E. Isr J Chem 1993, 33, 369; (b) Bühl, M. In Encyclopedia of Computational Chemistry; Schleyer, P. v. R., Ed.; Wiley: New York, 1998; p 1835.
18. McMahon, M. T.; deDios, A. C.; Godbout, N.; Salzmann, R.; Laws, D. D.; Le, H.; Havlin, R. H.; Oldfield, E. J Am Chem Soc 1998, 120, 4784.
19. Becke, A. D. Phys Rev A 1988, 38, 3098.
20. (a) Perdew, J. P. Phys Rev B 1986, 33, 8822; (b) Perdew, J. P. Phys Rev B 1986, 34, 7046.
21. (a) Wachters, A. J. H. J Chem Phys 1970, 52, 1033; (b) Hay, P. J. J Chem Phys 1977, 66, 4377.
22. (a) Gonzales, C.; Schlegel, H. B. J Chem Phys 1989, 90, 2154; (b) Gonzales, C.; Schlegel, H. B. J Phys Chem 1990, 94, 5523.
23. Ziegler, T. Can J Chem 1995, 73, 743.

24. Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frisch, M. J. J Chem Phys 1996, 104, 5497.
25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Head−Gordon, M.; Gonzales, C.; Pople, J. A. Gaussian 94; Gaussian Inc.: Pittsburgh, PA, 1995.
26. Becke, A. D. J Chem Phys 1993, 98, 5648.
27. Lee, C.; Yang, W.; Parr, R. G. Phys Rev B 1988, 37, 785.
28. Bühl, M. Chem Phys Lett 1997, 267, 251.
29. (a) Bader, R. W. F. Atoms In Molecules. A Quantum Theory; Clarendon Press: Oxford, UK, 1990; (b) Bader, R. W. F. Chem Rev 1991, 91, 893.
30. Popelier, P. L. A. Comput Phys Commun 1996, 93, 212.
31. Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. J Comput Chem 1983, 4, 294.
32. Bashirpoor, M.; Schmidt, H.; Schulzke, C.; Rehder, D. Chem Ber/Recueil 1997, 130, 651.
33. In a related Schiff-base complex with 2-butanol as the donor ligand, somewhat larger V−O separations are encountered up to 2.328(8) Å: Fulwood, R.; Schmidt, H.; Rehder, D. J Chem Soc Chem Commun 1995, 1443.
34. Rehder, D. In Metal Ions in Biological Systems; Sigel, H.; Sigel, A., Eds.; Marcel Dekker: New York, 1995; Vol. 31, p 1.
35. Griffith, W. P.; Wickins, T. D. J Chem Soc A 1966, 1087.
36. Harnung, S. E.; Larsen, E.; Pedersen, E. J. Acta Chem Scand 1993, 47, 674.
37. Only at lower pH with formation of VO_2^+ does the coordination number increase to six: Cruywagen, J. J.; Heyns, J. B. B.; Westra, A. N. Inorg Chem 1996, 35, 1556.
38. The same was previously found at the self-consistent field level employing small basis sets: Ribeiro−Claro, P. J. A.; Amado, A. M.; Teixeira−Dias, J. J. C. J Comput Chem 1996, 17, 1183.
39. In order to probe if a pentacoordinate form might be stabilized by medium effects due to the highly polar solvent, an optimization was also started in a spherical, polarizable continuum [(a) Kirkwood, J. G. J Chem Phys 1934, 2, 351; (b) Onsager, L. J Am Chem Soc 1936, 58, 1486; implementation in the Gaussian program: (c) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. J Am Chem Soc 1991, 113, 4776], employing the dielectric constant of water, which also resulted in dissociation of the water molecule from vanadium.
40. A referee pointed out that DFT usually underestimates weak donor−acceptor bonds and that MP2 would do a better job. However, at the MP2/I level **6a** also does not exist and optimizes to $\mathbf{5} \cdot H_2O$.
41. Krauss, M.; Basch, H. J Am Chem Soc 1992, 114, 3630.
42. Ultimately, molecular dynamics simulations should be performed for a sampling of the configuration space on the free energy surface. Polycyclic H-bonded motifs as in $\mathbf{5} \cdot H_2O$ and $\mathbf{5} \cdot 2H_2O$ are probably disfavored entropically.
43. Removal of the water molecule from **7a** affords $[V(O)_2(glygly)']^-$ (i.e., deprotonated **4**) with a computed $\delta(^{51}V) = -610$; the deshielding effect of a single solvent molecule is thus much smaller in this case than for **5**.
44. (a) Eckert, H.; Wachs, I. E. J Phys Chem 1989, 93, 6796; (b) Das, N.; Eckert, H.; Hu, H.; Wachs, I. E.; Walzer, J. F.; Feher, F. J. J Phys Chem 1993, 97, 8240; (c) Crans, D. C.; Felry, R. A.; Chen, H.; Eckert, H.; Das, N. Inorg Chem 1994, 33, 2427; (d) Lee, M.-H.; Heo, N. H.; Hayashi, S. Polyhedron 1998, 17, 55.
45. Direct assessment of theoretical ^{51}V shift tensors is difficult because of the lack of suitable experimental reference data. For the solid reaction product of vanadate with *tert*-butanol, presumably $VO(O\mathit{t}Bu)_3$, components $\delta_{ii} = -555$, -575, and -875 were reported (ref. 44c), which is in fair accord with the GIAO-B3LYP/I data for model compound $VO(OMe)_3$, $\delta_{ii} = -637$, -637, and -835.